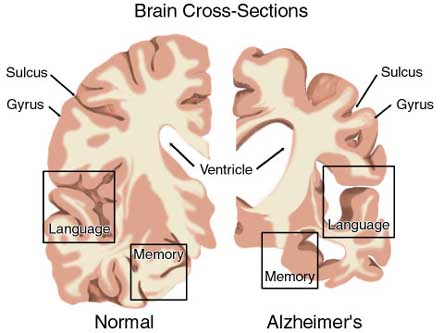
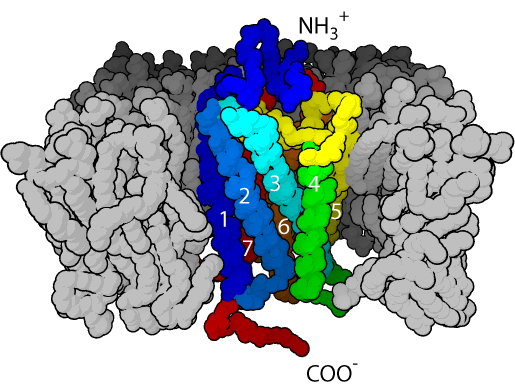
**Alzheimer Disease**

Families come to face the fact that one of their members has Alzheimer's in many ways. Husband or wives may begin to realize that their spouse is behaving differently, is sometimes unable to perform normal tasks, and has surprising lapses in memory. Extended families living together usually come to this same gradual realization. It is known that any person dreads to see a family member or friend with that of Alzheimer’s disease. The impact it has on anyone can be slow, painful, and stressful in that much patience and time needs to be given in order to take care of a person with this disease. A man by the name of Dr. Alois Alzheimer noticed a usual change in the brain tissue of a woman who died of a mental illness. He observed that her symptoms included language problems, a severe loss of memory, and irregular actions/behavior. After this woman died, Dr. Alzheimer examined her brain to later find many abnormal clumps (*amyloid plaques)* and bundles of fiber that were significantly tangled within the brain. It is known that plaques and tangles are two main aspects of this horrible disease. The third aspect is the loss of connections between nerve cells (neurons) in the brain. Scientist still don’t know what starts the Alzheimer’s disease process, but they do know that damage to the brain begins as many as 10 to 20 years before problems are noticeable. As more and more of these plaques and tangles form in particular brain areas, healthy neurons begin to work less efficiently. Overtime these neurons lose their ability to function and communicate with each other, and eventually die. This trend spreads to another part of the brain called the hippocampus, which is responsible for forming memories. As the death of neurons increases, affected brain regions begin to shrink. By the final stage of Alzheimer’s, damage is widespread and brain tissue has shrunk significantly. The final stage has the greatest impact on the person with the disease, as well as the people that care about that particular person.

**(Fig. 1) A brain cross-section that compares a normal brain to that of a brain affected with Alzheimer’s disease.**

Alzheimer’s disease is an irreversible, degenerative brain disease that slowly wipes out memory, thinking skills, and the ability to carry out simple tasks in life. In most cases, people with Alzheimer’s experience their first symptoms after the age of 60. Alzheimer’s disease is the most common cause of dementia (the loss of cognitive thinking functioning; which can later interfere with a person’s daily life and activities) among older people**.** Scientists don’t yet fully understand what causes Alzheimer’s disease, but it is understandable that it develops because of a complex series of events that take place in the brain over a long period of time. Likely causes of this disease can go hand-in-hand with lifestyle, environment, and genetic factors. The delay of getting Alzheimer’s disease varies from person to person given the fact that genetic make-ups are very different. There are a number of early signs and symptoms of AD. The most evident sign is loss of memory and other memory problems. Since Alzheimer’s disease is a very progressive disease, memory loss continues and changes in other cognitive abilities appear. Simple things such as forgetting names of family members, repeating statements and questions, poor judgment, mood swings, and trouble carrying out simple tasks allow for many people to be diagnosed in this first stage. In the second stage of Alzheimer’s disease damage occurs in areas of the brain that control reasoning, sensory processing, reasoning, and conscious thought. Memory loss and confusion increase, and people begin to have problems recognizing family and friends. They may be unable to learn new things, carry out tasks that involve multiple steps (such as getting dressed), or cope with new situations. They may have hallucinations, delusions, and paranoia, and may behave impulsively. By the final stage, plaques and tangles have spread throughout the brain and brain tissue has shrunk significantly. People with severe Alzheimer’s cannot communicate and are completely dependent on others for their care. Near the end, the person may be in bed most or all of the time as the body shuts down.

One main question that researchers are trying to answer is how the brain gets worse as a person’s age increases. Scientists are learning how age-related changes in the brain may harm neurons and contribute to Alzheimer’s damage. There is no cure available for Alzheimer and there is a lack of drug targets in this field but many recent targets have been discovered, released, and patented. Galapagos has recently been awarded U.S. patent 7,429,459 for the use of GPR3 in screening for Alzheimer’s drugs. On February 13, 2009 a company by the name of Galapagos revealed a key drug target for Alzheimer’s disease. This drug target is published in *Science* and is U.S. patent granted. ‘GPR3 is a promising drug target for developing a treatment for Alzheimer’s.’ Inhibition of GPR3 prevented the accumulation of beta-amyloid, a protein in the brains of Alzheimer’s patients that is believed to cause the disease. The article also shows that GPR3 levels are higher in the areas of the brain that are affected in Alzheimer’s patients. The activity of GPR3 can likely be inhibited with a small molecule drug. Taken together, GPR3 is a promising drug target for development of a treatment for Alzheimer’s disease.

**(Fig. 2) The seven-transmembrane α-helix structure of a G-protein-coupled receptor**

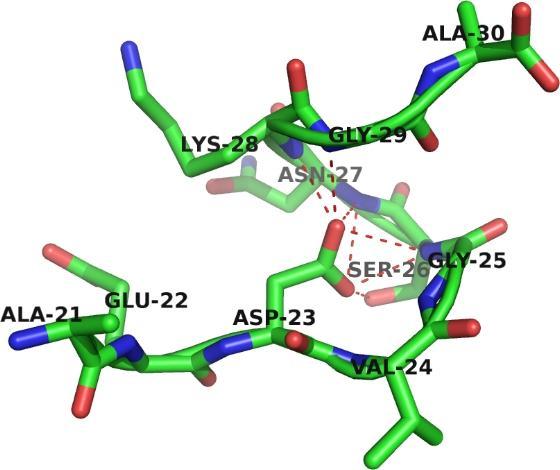
**Accumulation of the amyloid-β peptide (Aβ) is thought to represent a central problem in the pathogenesis of Alzheimer’s disease. This functional genomics effort identified the G protein–coupled receptor, GPR3, as a modulator of Aβ production. GPR3 has been mapped to a chromosomal locus associated with increased risk for Alzheimer’s disease; is highly expressed in hippocampus and cortex, regions of the brain that strongly correlate with Alzheimer’s disease progression; and thus represents an attractive drug target** (*Galapagos*). According to *ScienceDaily*, for some time, scientists have blamed Alzheimer's disease on a small molecule called amyloid beta protein (A beta) that leaves large gummy deposits in the brain. Recent studies suggest that these A beta proteins stick together to form “**floating toxic clumps that kill brain cells**”(*UCLA*). Now, UCLA scientists have identified a tiny loop in A-beta as the likely cause behind the adhesion process within the brain. The UCLA team found out that gene mutations in A-beta increase the loop's flexibility, causing it to join easily with loops from other A-beta proteins and form clumps. **The loop also appears in the region of the protein that regulates how, and how much A-beta is made. Current drugs treat the symptoms of Alzheimer's but not the disease's underlying cause. By shedding light on how toxic A-beta formations arise in the brain, the UCLA discovery could aid the design of new drugs that both block the production of A-beta and prevent it from clumping. Specific symptoms that go hand-in-hand with this protein are related to gamma secretase inhibitors which block proteins involved in the creation of amyloid beta, the main component of Alzheimer's. Patients cannot continuously take these drugs because nonstop inhibition of the gamma secretase enzyme has harmful side effects** (*UCLA*).One study had revealed that when physicians temporarily halted used of the inhibitors in humans, amyloid beta levels in the blood rush forward. An animal study suggested cessation of treatment also led to an amyloid beta increase in the brain. **Researchers have been watching for similar effects in current human clinical trials of gamma secretase inhibitors.** (*UCLA).*This particular peptide can be dissolved initially in water (approximately 6 mg/ml). With given precautions, it is said “**do not dissolve the lyophilized peptide directly into saline or buffer as the peptide will not be soluble. For maximal biological activity, it should be further diluted with PBS that does not contain calcium to 1 mg/ml and incubated at 37 °C for 4 days before adding to culture media at the final desired concentration**”(*Sigma)*.

**Molecular Formula:** C194H295N53O58S

**Molecular Weight:** 4,329.8 Da

**CAS Number:** 131438-7 9-4

**Structure:** Asp-Ala-Glu-Phe-Arg-His-Asp-Ser-Gly-Tyr-Glu-ValHis-His-Gln-Lys-Leu-Val-Phe-Phe-Ala-Glu-Asp-ValGly-Ser-Asn-Lys-Gly-Ala-Ile-Ile-Gly-Leu-Met-Val-GlyGly-Val-Val-OH



**(Fig. 3)Amyloid Protein Loop. Broken red lines indicate a loop in the amyloid B-protein that enables it to attach to other proteins and form clumps that kill brain cells. (Credit: Image courtesy of University of California)**

In the years to come, AD is expected to pose physical and emotional challenges for more and more families and other caregivers, in addition to those with the disease. The growing number of people with AD and the costs associated with the disease also will put a heavy economic burden on society. **“According to recent estimates, as many as 2.4 million to 5.1 million Americans have AD. Unless the disease can be effectively treated or prevented, the number of people with AD will increase significantly if current population trends continue. That’s because the risk of AD increases with age, and the U.S. population is aging. The number of people age 65 and older is expected to grow from 39 million in 2008 to 72 million in 2030, and the number of people with AD doubles for every 5-year interval beyond age 65.”** (*NIA).* One of the greatest unsolved mysteries of Alzheimer’s disease is why it largely strikes older adults; only time will provide the information that many scientists need.

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